Updates in Cardiorenal Syndrome

Wendy McCallum, MD, MS[a,*], Jeffrey M. Testani, MD, MTR[b]

KEYWORDS

• Cardiorenal syndrome • Acute decompensated heart failure • Venous congestion
• Neurohormonal activation

KEY POINTS

- Cardiorenal syndrome is an umbrella term that recognizes the interorgan relationship between the kidneys and the heart and how injury to one organ often leads to injury in the other
- The pathophysiology of cardiorenal syndrome is complex and heterogenous, but includes hemodynamic changes and neurohormonal upregulation among other etiologies
- Management for ADHF remains focused on decongestion with diuretics as well as neurohormonal modulation as a way to overcome the intense sodium and fluid avidity of the CRS.

INTRODUCTION

Among patients with heart failure, there is a high prevalence of chronic kidney disease (CKD), with both disorders sharing significant common risk factors. Dysfunction in both the heart and kidney has been collectively grouped under the term cardiorenal syndrome (CRS). There have been attempts to define CRS by subtypes, according to which organ—the heart versus the kidney—is believed to be the culprit organ triggering dysfunction in the other. However, in most clinical settings, it is challenging to delineate because the pathophysiology is closely intertwined and pathways remain poorly understood. For the purposes of this review in CRS, we will primarily focus on 2 patient populations—patients with chronic heart failure in the ambulatory setting and patients admitted to the hospital for acute decompensated heart failure (ADHF)—and review the kidney complications that can arise in these 2 clinical scenarios and updates in pharmacologic treatment options.

[a] Division of Nephrology, Tufts Medical Center, 800 Washington Street, Box 391, Boston, MA 02111, USA; [b] Division of Cardiovascular Medicine, Yale School of Medicine, PO Box 208017, New Haven, CT 06520, USA
* Corresponding author. 800 Washington Street, Box 391, Boston, MA 02111, USA
E-mail address: wmccallum@tuftsmedicalcenter.org

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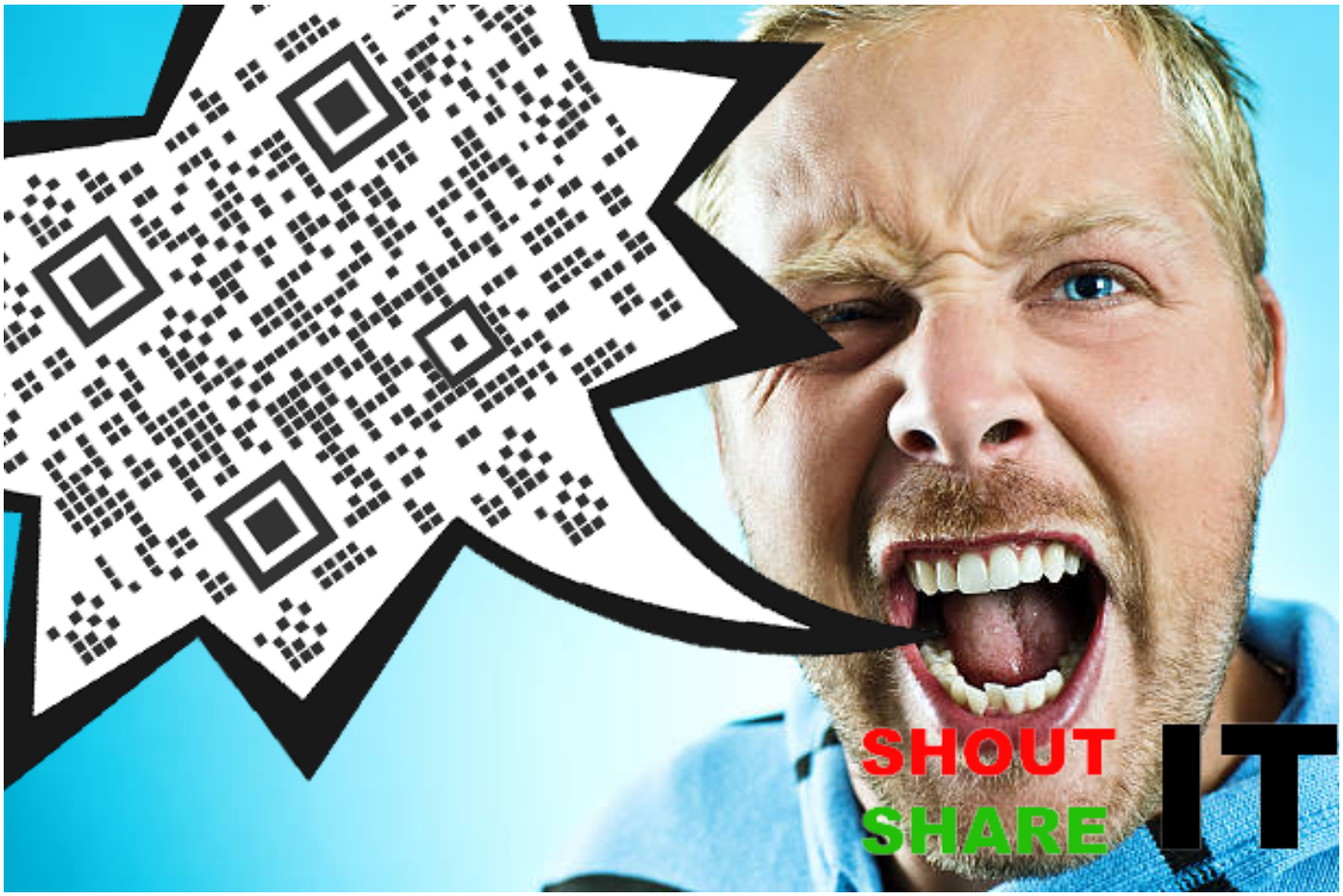
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EPIDEMIOLOGY AND PROGNOSIS

The prevalence of heart failure is estimated around 64.3 million adults worldwide.[1] Among patients with heart failure, the prevalence of CKD, as defined by an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, is upwards of 50%.[2] The presence of CKD is one of the most powerful risk factors for mortality and cardiovascular events among patients with heart failure.[3] Multiple observational studies and post-hoc analyses have shown a graded association between eGFR and risk for mortality, with risks highest among those with the lowest eGFR.[4]

Fluctuations in eGFR are also very commonly encountered among patients with heart failure. In many other patient populations, an acute decline in eGFR is often interpreted as a clinical cue for either decline in clinical status or a sign of kidney injury in reaction to drugs or other substances. However, given the frequent fluid shifts and medication-associated hemodynamic declines in eGFR that can be observed with many classes of cardioprotective medications (such as with renin-angiotensin-aldosterone system [RAAS] inhibitors), interpreting acute eGFR declines among patients with heart failure can be challenging. For example, among patients admitted for ADHF, the prevalence of acute eGFR declines has been shown to be around 20% to 30%.[5] Unlike baseline reduced eGFR, these acute eGFR changes are not as consistently associated with adverse clinical outcomes. Particularly if the acute eGFR decline is sustained after an intervention that is otherwise protective in heart failure—whether it is diuresis for ADHF or initiation of a RAAS inhibitor—the cardiovascular benefits of the intervention outweigh any risk associated with the eGFR decline. Post-hoc analysis of the ESCAPE trial,[6] which randomized patients admitted for ADHF to treatment guided by a pulmonary artery catheter versus without, showed that acute declines in eGFR that occurred together with simultaneous evidence of hemoconcentration (as a proxy of decongestion), were not associated with greater risks of mortality and rehospitalization for ADHF.[7] In contrast, if an acute decline in eGFR is sustained outside of interventions such as diuresis or initiation of RAAS inhibitor—such as ongoing congestion in the hospital—the acute eGFR decline likely signals a decline in clinical status and thereby associated with adverse outcomes such as higher risk of mortality and re-hospitalization for heart failure. A number of studies drawn from different ADHF trials have shown consistent findings, reiterating the importance of context for interpreting acute eGFR declines among patients with heart failure.[8,9]

PATHOPHYSIOLOGY AND COMPLICATIONS

The mechanisms underlying the pathophysiology of the CRS are not well understood, but most likely involve multiple bi-directional pathways centering on arterial underfilling, venous congestion, and neurohormonal activation.

Arterial Underfilling

While historically it had been believed that low cardiac output was the primary driver of low GFR in the CRS, there have since been multiple observational studies showing no direct association between low cardiac output and either reduced baseline eGFR or acute declines in eGFR.[10,11] There have also been several trials of therapeutic agents that increase cardiac output, without clear evidence of any connection between increasing the cardiac output and an increase in eGFR. In the OPTIME-CHF trial, in which 951 patients with ADHF were randomized to treatment with 48-h of milrinone versus placebo, the use of milrinone as a positive inotropic agent did not show any associated increases in eGFR.[12,13] Some of the inotropic effects could have been off-set by the vasodilating effects of milrinone, with about 10% having sustained

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hypotension (systolic blood pressure<80 mm Hg) compared to 3% in the placebo arm. However, the GALACTIC trial, a large randomized control trial of the selective cardiac myosin activator, omecamtiv mecarbil, also failed to show any increases in eGFR in the treatment arm.[14] Of the 4120 patients randomized to the omecamtiv mecarbil group, a drug that directly augments cardiac sarcomere function and known to improve stroke volume, there was no change in serum creatinine at 48 weeks and no difference between the treatment arm and placebo arm (creatinine change of 0.06 ± 0.39 mg/dL in the treatment arm vs 0.05 ± 0.38 mg/dL in the placebo arm). In other words, low cardiac output in ADHF might be triggering a cascade of maladaptive responses, but overall does not seem to be the main driver of declines in eGFR on a population level. On the other hand, there are certain scenarios such as cardiogenic shock, an extreme case of low cardiac output and of low organ perfusion that leads to organ ischemia, including the kidney, where this relationship is likely highly relevant.

Venous Congestion

There has been literature suggesting that in cross-sectional studies, venous congestion as measured by elevated central venous pressures (CVP), can be associated with low baseline kidney function.[11,15] However, this has been an inconsistent finding and on average across studies rarely is CVP anything more than weakly associated with renal function. The challenge remains even when evaluating the weak association, more severe venous congestion in ADHF is often associated with more severe heart failure, making it very difficult to isolate whether the congestion itself is associated with lower kidney function, or whether patients with more advanced and severe heart failure have more diuretic resistance and worse kidney function by virtue of having more advanced cardiac disease. Furthermore, in terms of longitudinal changes in eGFR, neither higher CVP nor changes in CVP have been associated with either declines or increases in eGFR over the course of hospitalization for ADHF.[11,16,17] Overall, however, congestion is consistently associated with poor survival and re-hospitalization for ADHF, making decongestion and maintaining euvolemia an important priority from a cardiovascular perspective, regardless of whether the eGFR decreases or increases. While decongestion has not been associated with improvements in eGFR, one observational study has at least shown no evidence of longer term kidney function declines among those with more rapid in-hospital decongestion.[18] While the congestion itself may not be the primary factor driving declines in kidney function, such patients with greater excess venous congestion and diminished ability to respond to diuretics will be at much higher risk of mortality and morbidity, including declines in kidney function.

Neurohormonal Activity, Sodium, and Water Avidity

The hallmark of the CRS is intense sodium and water avidity, leading to fluid retention and diminished urinary response to diuretics. There are a number of neurohormonal pathways that drive kidney sodium and water avidity, including components of the RAAS such as angiotensin II, aldosterone, as well as the sympathetic nervous system and vasopressin. Arterial underfilling in heart failure will stimulate baroreceptors to trigger RAAS stimulation; on the other hand, some animal studies of renal vein ligation have also shown an increase in RAAS activity and urine sodium avidity with venous renal congestion as well.[19] Another important trigger for RAAS is low tubular fluid chloride delivery sensed by the macula densa. Observational studies have shown that renin levels are higher among patients with hypochloremia, with plasma renin levels correlated negatively with serum chloride values even after adjustment for baseline kidney function.[20]

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The other important neurohormonal axis is the natriuretic peptide system. Volume overload and myocardial stretch have been shown to release natriuretic peptides, which counteract many of the sodium avidity triggers described above. Natriuretic peptide receptors in the kidney will stimulate sodium excretion and increase GFR. Administration of recombinant natriuretic peptides such as nesiritide showed improvements in cardiac and renal hemodynamics in some short-term studies[21,22]; however, in larger trials among patients with ADHF, there were no improvements in either urine output, eGFR, or cardiovascular outcomes.[23,24]

DIAGNOSTIC STRATEGIES

Evaluations of Kidney Function: Blood Biomarkers

There are many nuances to how to evaluate kidney function among patients with heart failure. There are no current biomarkers that are able to capture all the various functions that the kidney accomplishes—in other words, not just glomerular filtration, but also tubular electrolyte and water handling and endocrine functions. Serum creatinine is the most widely available biomarker and remains the backbone of GFR estimating equations including the updated CKD-EPI 2021 formula.[25] However, it is important to acknowledge the limitations of creatinine, particularly factors that can impact the value of serum creatinine outside of GFR. Creatinine is a by-product of muscle metabolism, and therefore patients with low muscle mass can have low values of serum creatinine that can lead to over-estimates of their kidney function. Particularly for patients with heart failure, among whom there is a high prevalence of sarcopenia and muscle loss, an eGFR based on creatinine can be an overestimate of the measured GFR. Several medications, such as trimethoprim or cimetidine, can block the tubular secretion of creatinine and conversely lead to an underestimate of the GFR. These nuances to interpretation can become important when patients are being considered candidates for certain medication classes, antibiotic dosing, and candidacy for advanced therapies.

Another biomarker that has become more widely available for clinical use is cystatin C, a low molecular weight protein ubiquitously expressed throughout all nucleated cells. For the general population, it has been recommended to incorporate both creatinine and cystatin C into the CKD-EPI 2021 formula for better accuracy.[26] While cystatin C may be less affected by muscle mass relative to creatinine, it can be affected by other factors such as thyroid disease, steroid use, smoking, and inflammation.[27] The nuances of interpretation of cystatin C among patients with heart failure is still an area that needs greater evaluation.

In terms of monitoring changes in kidney function, a rise in serum creatinine is a relatively delayed finding in intrinsic kidney injury. Furthermore, a rise in creatinine can also occur when there are hemodynamic changes to GFR, without injury. Among patients with heart failure, who are prone to hemodynamic fluid shifts, but also at risk for ischemic tubular injury, an acute rise in serum creatinine becomes a challenging finding to interpret. In a post-hoc analysis of the ROSE-AHF study, levels of tubular injury biomarkers—including *N*-acetyl-β-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL)—did not change with protocol-driven diuresis (median urine output of 8.4 L over 72-h), whereas the eGFR decreased by $\geq$ 20% in 21% of patients.[28] There was also no association between eGFR decline and increase in the tubular injury biomarkers, suggesting that these were not signs of intrinsic kidney injury. However, other studies have observed elevation in levels of NGAL with diuresis that were not associated with mortality events or development of kidney failure.[29] With the inconsistency of results, none

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of the tubular injury biomarkers are being recommended for routine clinical use at this time.

Evaluations of Kidney Function: Urinary Tests

Examination of the urine can be a helpful piece of clinical data in the evaluation of the CRS. A urinalysis (and if possible, examination of the urine sediment) is classically believed to be bland (ie, no red blood cells or white blood cells or casts) if the decline in kidney function is in the setting of CRS. On the other hand, any other findings on urinalysis may prompt further investigation and reveal a number of potential etiologies of intrinsic kidney disease such as diabetic nephropathy, interstitial nephritis, acute tubular necrosis, or vasculitis. However, it should be pointed out that since there is no gold standard diagnostic test for CRS, it is challenging to know if an active sediment is in fact never seen in CRS. Particularly among patients with both heart failure and CKD with proteinuria, it would be important not to miss diagnoses such as amyloidosis or Fabry disease, which would lead to a significant change in management. Quantification of proteinuria and albuminuria with the use of spot samples or 24-h urine collection is also helpful. Among patients with ADHF, one study repeated spot urine albumin:creatinine ratios daily over the first 7-days of hospitalization to assess whether the degree of albuminuria changes with decongestion.[30] It showed that the prevalence of albuminuria diminished over time with diuresis; however, an important caveat is that the quantification using spot samples can vary substantially depending on the degree of urinary creatinine excretion measured on each spot sample, which may or may not change during ADHF therapy. Assessment of whether albuminuria changes with decongestion, when measured using 24-h urine collections, would be interesting.

Evaluation of urine electrolytes, in particular urinary sodium, has also become incorporated as a way to evaluate diuretic response among patients admitted for ADHF. A low spot urine sodium obtained ~2 hours after dosing of diuretics can be a good predictor of poor diuretic response and can help guide diuretic dose escalation.[31]

Evaluations of Kidney Function: Imaging Modalities

Imaging of the kidneys can provide some helpful information as well. At least among patients with general CKD, ultrasound findings of echogenicity correlated best with histopathologic findings of chronicity and scarring.[32] Presumably, this correlation could be extrapolated to patients with heart failure as well but has not been formally evaluated. Point-of-care ultrasound, which has been increasingly incorporated into certain clinical settings including the emergency department and intensive care unit, has been investigated as a noninvasive modality to assess venous congestion and aid decision-making regarding diuresis. Patterns of blood flow in the inferior vena cava, hepatic vein, portal vein, and intrarenal veins have been identified as evidence of venous congestion that correlates with elevated central venous pressures.[33] There has also been some interest in using patterns of intrarenal venous blood flow as a prognostic tool,[34] but whether it adds more information on top of other clinical markers of venous congestion is still unknown.

MANAGEMENT—CHRONIC HEART FAILURE

For the majority of patients with both heart failure and CKD, with the bi-directional crosstalk from both organs, therapeutic management can focus on therapies that will be cardiac-specific, kidney-specific, or common to both. There have been a number of landmark trials that have changed the landscape of medical management for patients with chronic heart failure and CKD, particularly for heart failure with reduced

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ejection fraction (HFrEF). For the purposes of this review, we will focus on major classes of agents that have beneficial effects on both the heart and the kidney, including angiotensin receptor/neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) including non-steroidal MRAs, and sodium-glucose contransporter-2 (SGLT2) inhibitors.

Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers

Activation of the RAAS hormonal pathway is a compensatory mechanism after cardiac injury, as well as in the setting of perceived arterial underfilling. In terms of the kidney, RAAS will lead to preferential vasoconstriction of the efferent arteriole, increasing intraglomerular pressure. Angiotensin II and aldosterone are also powerful stimulants for sodium reabsorption along multiple points of the renal tubules. Blockade of the RAAS hormonal pathway remains a cornerstone in the management of HFrEF. Multiple landmark trials have shown mortality and cardiovascular benefit in HFrEF (**Table 1**), and blockade using ACEI or ARB also plays a key central role in the management of proteinuric CKD. Because of the many shared comorbidities between CKD and HFpEF—namely diabetes and hypertension—the majority of patients with HFpEF will also meet indications for use of RAAS blockade as demonstrated by a Swedish registry study. Of 16,216 patients enrolled in the Swedish Heart Failure Registry with an EF $\geq$ 40%, 56% were using an ACEI and 20% were using an ARB.[35] In summary, even if trials of RAAS blockade specifically for cardiovascular benefits in HFpEF did not show survival benefit,[36,37] it has been a reasonable recommendation to use these agents to manage other comorbidities such as hypertension or proteinuria.

As alluded to above, an acute decrease in eGFR can be observed after initiating an ACEI or ARB due to the preferential vasodilation of the efferent arteriole leading to a hemodynamic eGFR decline. For example, the SOLVD trials, which randomized patients with HFrEF to treatment with enalapril versus placebo, had collectively about 10% of patients with an acute decline of >20% eGFR decline at 2-weeks. Among the patients with an acute eGFR decline after the initiation of enalapril, the treatment still showed a significant reduction in risk for mortality and hospitalization for ADHF when compared to patients with acute eGFR decline after randomization to placebo.[38,39] Even when compared to patients randomized to placebo without any acute eGFR decline (presuming all the acute eGFR decline can be assumed to be medication-drive), randomization to enalapril still showed clinical benefits.[39]

Angiotensin Receptor/Neprilysin Inhibitor

Natriuretic peptide release is triggered by numerous stimuli, including myocardial stretch from volume overload or other mechanical stressors to the heart. In the kidney, natriuretic peptides counteract many of the actions of RAAS by antagonizing sodium reabsorption and vasoconstriction, resulting in natriuresis. However, infusion of recombinant natriuretic peptides has not shown any benefits such as increase in urinary output or increases in eGFR,[24] nor differences in mortality.[23] Inhibition of neprilysin, a metalloproteinase that degrades natriuretic peptides, has on the other hand been shown to be beneficial for cardiovascular outcomes among patients with HFrEF when used in combination with ARB. The PARADIGM trial randomized 8442 patients with HFrEF to treatment with either sacubitril/valsartan or enalapril, with a decreased risk of cardiovascular death and HF hospitalization observed in the sacubitril/valsartan arm.[40] While randomization to sacubitril/valsartan did not reach statistical significance for benefit in terms of the pre-specified kidney composite endpoint (kidney failure, $\geq$50% eGFR decline, or eGFR decrease by > 30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2), there was a slower

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Table 1
Examples of landmark trials that have influenced pharmacological management of patients with heart failure with reduced ejection fraction

Class of Drug	Trial	n	Intervention	Kidney Exclusion Criteria	Primary Outcome	Kidney Outcome[a]
ARNI	PARADIGM[40]	8442	Sacubitril/valsartan vs enalapril	eGFR <30 mL/min/1.73 m^2	HR 0.80 (0.73, 0.87) for composite of CV death or HF hospitalization	eGFR decline by −1.61 mL/min/1.73 m^2/year in treatment arm vs −2.04 mL/min/1.73 m^2/year in the placebo arm ($P < .001$)[41] HR 0.86 (0.65, 1.13) for kidney failure, ≥50% eGFR decline, or eGFR decrease by > 30 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2
ACEI	SOLVD- Treatment[69]	2569	Enalapril vs placebo	Cr > 2 mg/dL	RR 0.84 (0.74, 0.95) for all-cause mortality RR 0.74 (0.66, 0.82) for composite of death or HF hospitalization	Initial decline in eGFR in the enalapril arm, without significant difference in longer-term slope thereafter (−0.84 [-1.24, −0.43] vs −1.36 [-1.77, −0.94] mL/min/1.73 m^2/yr in the enalapril and placebo arms, respectively)[70]
ACEI	SOLVD-Prevention[71]	4228	Enalapril vs placebo	Cr > 2 mg/dL	RR 0.92 (0.79, 1.08) for all-cause mortality RR 0.64 (0.54, 0.78) for HF hospitalization	Initial decline in eGFR in the enalapril arm, without significant difference in longer-term slope thereafter (−1.27 [-1.56, −0.99] vs −1.37 [-1.65, −1.07] mL/min/1.73 m^2/year in the enalapril and placebo arms, respectively)[70]

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Table 1
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Class of Drug	Trial	n	Intervention	Kidney Exclusion Criteria	Primary Outcome	Kidney Outcome[a]
MRA	EMPHASIS-HF[72]	2737	Eplerenone vs placebo	eGFR <30 mL/min/1.73 m^2	HR 0.63 (0.54, 0.74) for composite of CV death or HF hospitalization	Initial faster rate of decline in eGFR in the eplerenone arm (−0.288 mL/min/1.73 m^2/year [-0.395, −0.182]) than placebo arm (−0.066 mL/min/1.73 m^2/year [-0.174, −0.042]) that was maintained through the trial[73]
MRA	EPHESUS[74]	6632	Eplerenone vs placebo	Cr > 2.5 mg/dL and K > 5 mmol/L	RR 0.85 (0.75, 0.96) for all-cause mortality	Initial decline in eGFR in the eplerenone arm that was maintained through the trial (adjusted mean difference of −1.4 mL/min/1.73 m^2)
SGLT2i	DAPA-HF[75]	4744	Dapagliflozin vs placebo	eGFR <30 mL/min/1.73 m^2	HR 0.74 (0.65, 0.85) for composite of worsening HF or CV death	eGFR decline by −1.09 mL/min/1.73 m^2/year in treatment arm vs −2.85 mL/min/1.73m2/year in the placebo arm (P < .001) HR 0.71 (0.44, 1.16) for renal composite
SGLT2i	EMPEROR-Reduced[76]	3730	Empagliflozin vs placebo	eGFR <20 mL/min/1.73 m^2	HR 0.75 (0.65, 0.86) for composite of CV death or HF hospitalization	eGFR decline by −0.55 mL/min/1.73 m^2/year in treatment arm vs −2.28 mL/min/1.73m2/year in the placebo arm (P < .001)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; K, potassium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

[a] Some kidney endpoints were prespecified endpoints from the original trial, and some were from post-hoc analyses; unless separate citation is included, the endpoint was from the original trial.

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rate of decrease in eGFR in the sacubitril/valsartan arm. Over the course of follow-up, the eGFR decreased by −1.61 mL/min/1.73 m^2/year (95% CI -1.77 to −1.44 mL/min/1.73 m^2/year) among those randomized to sacubitril/valsartan compared to −2.04 mL/min/1.73 m^2/year (95% CI -2.21 to −1.88 mL/min/1.73 m^2/year; $P < .001$) among those randomized to placebo[41] (see **Table 1**). Guidelines have incorporated the use of ARNI as first-line recommendation for the management of HFrEF, as long as tolerated from a blood pressure perspective.[42]

In contrast, the PARAGON study, which randomized 4822 patients with HFpEF to treatment with sacubitril/valsartan vs valsartan, only showed a trend toward benefit against cardiovascular outcomes.[43] However, randomization to the sacubitril/valsartan arm showed a 50% decreased risk of a kidney composite outcome of kidney-related death, development of kidney failure or >50% decline in eGFR (HR = 0.50, 95% CI 0.33, 0.77).[44] Furthermore, in a recent analysis of the pooled PARAGON and PARADIGM trials examining this set of composite renal outcomes (slightly modified from the pre-specified outcomes), randomization to sacubitril/valsartan was also associated with decreased risk of the composite outcome defined as ≥50% eGFR decline or development of kidney failure or death due to renal causes (HR = 0.56, 95% CI 0.42, 0.75).[45]

Mineralocorticoid Receptor Antagonists

In the heart, aldosterone has been shown to accelerate pro-fibrotic pathways which lead to hypertrophy, fibrosis, and adverse remodeling. Similarly, in the kidney, aldosterone has been associated with fibrosis with increased tissue production of transforming growth factor beta and fibronectin.[46] Agents such as spironolactone and eplerenone competitively block mineralicorticoid receptors, inhibiting the action of aldosterone. Trials among patients with HFrEF and patients with reduced EF post-myocardial infarction have all shown mortality and cardiovascular benefits with treatment with MRA (see **Table 1**). For patients with HFpEF, the Aldo-DHF trial, which randomized 422 patients with EF ≥ 50% to treatment with spironolactone versus placebo, showed improvement in parameters of diastolic function over the 12-month follow-up.[47] The TOPCAT trial, which included 3445 patients with preserved EF, showed a reduction in the primary outcome of the composite of death, aborted CV death, and HF hospitalization among those randomized to spironolactone over placebo, but it did not meet statistical significance (HR 0.89 [95% CI 0.77, 1.04].[48] However, post-hoc analyses limited to the 1767 patients enrolled in the Americas showed efficacy with spironolactone (HR 0.82 [95% CI 0.69, 0.98]); therefore, guidelines have suggested that there could be potential efficacy for patients with HFpEF.[42]

Given the increased risk of hyperkalemia with treatment with MRAs, as well as fear of hyperkalemia, 2 approaches have been studied: (1) whether continuation of MRAs together with potassium-binding agents is efficacious and safe, and (2) to evaluate non-steroidal MRAs with the belief that they cause less hyperkalemia. The DIAMOND trial included 878 patients with HFrEF with eGFR>30 mL/min/1.73 m^2 and hyperkalemia (defined as 2 serum potassium values of >5 mmol/L) while taking an ARNI, ACEI, ARB, and/or MRA.[49] Patients were randomized to either patiromer or placebo, while concurrently optimizing RAAS inhibitor therapy including up-titration of the MRA dose up to 50 mg per day. The trial showed that randomization to patiromir was successful in reducing serum potassium levels (between-group difference of −0.10 mmol/L [-0.13, −0.07] in potassium), and in the run-in phase most patients were able to achieve target doses of RAAS inhibitor therapy and MRA. In terms of the theoretical reduction in hyperkalemia risk associated with the non-steroidal MRA finerenone, it has not yet been studied in the heart failure population. The currently enrolling trial

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FINEARTS-HF trial (NCT04435626) will be examining finerenone among patients with CKD and HFpEF.

SGLT2 Inhibitors

The sodium-glucose cotransporter-2 reabsorbs glucose and sodium in the proximal tubule of the kidney, and had been initially studied as a target for hypoglycemic agents. Through a thus-far unclear mechanism, blockade of the SGLT2 leads to a wide range of significantly improved clinical outcomes, including overall survival, cardiovascular outcomes, HF hospitalizations, and kidney failure. The use of SGLT2i has become incorporated as first-line therapy in guidelines for both heart failure[42,50] as well as for diabetic kidney disease[51] and other subtypes of proteinuric glomerular disease.[52] With the growing list of patient populations who meet indications for the initiation of SGLT2i—patients with diabetes, diabetic kidney disease with albuminuria, non-diabetic kidney disease with albuminuria (and perhaps soon even without albuminuria), HFrEF, HFpEF and patients with diabetes—there is increased focus on barriers to implementation such as awareness and insurance costs. Particularly among patients with HFpEF, it has become an important class of medications to add to the limited available armamentarium.[53]

MANAGEMENT—ACUTE DECOMPENSATED HEART FAILURE

Hospitalizations for ADHF have accounted for approximately over 1 million hospitalizations in the United States annually,[54] representing a substantial healthcare burden. Most hospitalizations are driven by symptoms of volume overload, and strategies for decongestion remain the mainstay of management for patients admitted with ADHF. Evaluation should include assessment for factors that may have precipitated the ADHF, including acute coronary syndrome, arrhythmias, valvular disease, acute infection, or nonadherence with medication regimens. As for management, many therapeutic agents and strategies for ADHF—including agents to increase cardiac output, antagonize vasoconstriction, and increase urine output and GFR—have been developed but few have shown efficacy in larger trials to improve mortality or rehospitalization for ADHF. Management strategies for ADHF thus remain centered on decongestion and overcoming diuretic resistance, with the caveat that patients that decompensate further into cardiogenic shock would require additional means to restore end-organ perfusion.

Loop Diuretics

Intravenous loop diuretic therapy, which blocks the Na-K-2Cl channel in the kidney's loop of Henle, remains the backbone of decongestive strategies for ADHF. Based on results from the DOSE trial, which showed a trend toward more rapid symptom improvement with high dose over low dose strategies,[55] most clinical practice guidelines recommend initiating an intravenous dose that is 2 times the home daily dose.[42] There was no difference in bolus or continuous dosing. The important goal is to focus on up-titration of dosing within the initial 24-h, using spot urine sodium and/or hourly urine output as data to guide dosing. The European Society of Cardiology has published a position statement recommending a doubling of loop diuretic dose if the spot urine sodium at 2-h post diuretic is < 50 meq/L or the urine output is < 100 mL/h at 6-h post diuretic administration.[31]

Thiazide Diuretics

Thiazide diuretics, which block the Na-Cl cotransporter in the distal convoluted tubule, are important agents to use in combination with loop diuretics. They can be a

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particularly important class of agents because chronic use of loop diuretics has been shown to lead to distal tubular hypertrophy and increases the abundance of Na-Cl cotransporters.[56] The efficacy of using hydrochlorothiazide combined with a loop diuretic was examined in the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial, which randomized 230 patients admitted for ADHF to either thiazide plus loop or loop diuretic alone.[57] The trial showed greater weight loss achieved in the combined arm (−2.3 kg vs −1.5 kg) at 72-h. In contrast to classic teaching, thiazide diuretics—including oral metolazone, oral chlorthalidone, and intravenous chlorothiazide—can be effective at low GFR as well.[58] There can be significant potassium wasting with thiazide diuretics, which would need careful monitoring and repletion.

Mineralocorticoid Receptor Antagonists

Spironolactone and eplerenone act as competitive antagonists of the mineralocorticoid receptor, and are recommended for use in chronic ambulatory management of HFrEF. While they have consistently been shown to reduce risks of mortality and adverse CV outcomes in trials among chronic ambulatory heart failure patient populations, they can play a role as potassium-sparing diuretics for select ADHF patients as well. Even though the ATHENA trial, which randomized 360 patients with ADHF to treatment with high-dose spironolactone (100 mg) versus placebo or low-dose spironolactone (25 mg), did not show a significant difference in urine outcome or weight loss in the hospital, it also did not show any concerns regarding hyperkalemia or eGFR decline.[59] Some of this is related to what was likely inadequate dosing, given the short duration of the trial (4 days) vs the long half-life of the active metabolite of spironolactone, canrenone. Among patients with significant urinary potassium wasting and hypokalemia with diuretic therapy, addition of MRAs may be helpful.

Acetazolamide

Acetazolamide, an inhibitor of carbonic anhydrase, with a site of action primarily in the proximal tubule of the kidney, has generally been incorporated as a diuretic in cases of significant metabolic alkalosis. Blockade of carbonic anhydrase with acetazolamide reduces proton cycling and thereby sodium reabsorption via the sodium/hydrogen exchanger, leading to greater natriuresis. The ADVOR trial, which randomized 519 patients with ADHF to treatment with acetazolamide plus loop diuretic versus placebo plus loop diuretic, showed more rapid decongestion in the treatment arm by 3 days.[60] Notably, augmentation of diuresis/natriuresis was overall modest with 500 mL (95% CI, 200 mL to 800 mL) of additional fluid loss and 98 mmol (95% CI, 56 mmol to 140 mmol) of urine sodium over the 2-day study intervention. There was no significant difference in 3-month mortality or rehospitalization for ADHF, and important to recognize that the trial did not include the use of thiazides or SGLT2 inhibitors.

Vasopressin Antagonists

Tolvaptan, a selective vasopressin V2 antagonist, blocks the insertion of aquaporins into the distal tubule of the kidney and leads to aquaresis. The EVEREST trial, which randomized 4133 patients admitted for ADHF to treatment with tolvaptan versus placebo in addition to standard therapy showed greater weight loss in the tolvaptan arm.[61] However, there was no evidence of benefit in terms of mortality or rehospitalization for ADHF. In a *post-hoc* analysis, there was a cardiovascular benefit among patients with hyponatremia as defined by sodium <130 mmol/L.[62] Addition of tolvaptan could be considered among patients needing additional decongestion and hyponatremia.

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Table 2
Examples of trials that have examined pharmacological agents for the management of patients with heart failure with preserved ejection fraction

Class of Drug	Trial	n	Intervention	Kidney Exclusion Criteria	Primary Outcome	Kidney Outcome[a]
ARNI	PARAGON-HF[43]	4822	Sacubitril-valsartan vs valsartan	eGFR <30 mL/min/1.73 m^2	RR 0.87 (0.75, 1.01) for composite of CV death or HF hospitalization	HR 0.50 (0.33, 0.77) for composite of death from renal failure, ESKD, or $\geq$50% eGFR decline[44]
ARB	CHARM-Preserved[36]	3023	Candesartan vs placebo	Cr $\geq$ 3 mg/dL	HR 0.89 (0.77, 1.03) for composite of CV death or HF hospitalization	Greater decrease in eGFR at 26-mo in the candesartan arm (-9.2 ± 21 mL/min/1.73 m^2) vs placebo arm (-3.8 ± 20 mL/min/1.73 m^2); $P = .04$
MRA	TOPCAT[7]	3445	Spironolactone vs placebo	eGFR <30 mL/min/1.73 m^2 or Cr > 2.5 mg/dL	HR 0.89 (0.77, 1.04) for composite of CV death, HF hospitalization, or aborted cardiac arrest	Doubling of serum Cr to a value beyond the upper reference limit was more common in the spironolactone arm than placebo arm (10.2% vs 7.0%, $P < .001$)
SGLT2i	EMPEROR-Preserved[53]	5988	Empagliflozin vs placebo	eGFR <20 mL/min/1.73 m^2	HR 0.79 (0.69, 0.90) for composite of CV death or HF hospitalization	eGFR decline by -1.25 mL/min/1.73 m^2/year in treatment arm vs -2.62 mL/min/1.73 m^2/year in the placebo arm ($P < .001$)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium/glucose cotransporter-2 inhibitor.

[a] Some kidney endpoints were prespecified endpoints from the original trial, and some were from post-hoc analyses; unless separate citation is included, the endpoint was from the original trial.

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Invasive Methods for Decongestion

If a patient remains volume overloaded despite up-titration of available pharmacologic agents, or there develops the requirement for rapid fluid removal or electrolyte and/or uremic indications for renal replacement therapy (RTT), management could include escalation to invasive means of fluid removal including ultrafiltration or RTT. There have been several trials investigating ultrafiltration versus stepped diuretic therapy suggesting an improvement in rehospitalization; however, this was not observed in all trials.[63–65] Clinical guidance has remained to use pharmacologic therapy until no further options outside of invasive means such as ultrafiltration or RRT for volume removal.

Opportunity to Establish Chronic Heart Failure Therapy

There have been a number of pharmacologic agents incorporated into guideline-directed therapy particularly for chronic ambulatory patients, as outlined in **Table 1** and **Table 2**. However, initiation and maintenance of target dosing of these agents have been shown to fall short in clinical practice.[66] Both patient and clinician apprehension regarding adverse effects—acute eGFR declines, electrolyte abnormalities, blood pressure changes—likely play a large role in the clinical inertia behind slow implementation in the outpatient setting. Studies of various agents have examined the safety and efficacy of initiation of agents such as ARNIs and SGLT2 inhibitors prior to discharge from hospitalization for ADHF and have mostly shown that inpatient initiation is safe.[67,68] Such a strategy of initiation while under close monitoring in the hospital may help address some of the issues of implementation.

SUMMARY

The CRS is a term that refers to a collection of disorders involving both the heart and kidneys, encompassing multi-directional pathways between the 2 organs mediated through low arterial perfusion, venous congestion, and neurohormonal activation. There have been a number of trials of pharmacological agents that have demonstrated improved cardiovascular and kidney outcomes, particularly among chronic ambulatory patients. Management for ADHF remains focused on decongestion and ways to overcome the intense sodium and fluid avidity of the CRS.

CLINICS CARE POINTS

- A low spot urine sodium obtained ~2 hours after dosing of diuretics can be a good predictor of poor diuretic response and can help guide diuretic dose escalation.31
- Patients with cardiorenal syndrome often have diuretic resistance, and will require escalating doses of loop diuretics. When uptitrating the dose of these agents, a doubling of the prior dose should be considered as the next step.
- Neurohormonal modulation in cardiorenal syndrome involves therapy with several classes of therapeutics that have beneficial effects on both the heart and the kidney, these include angiotensin receptor/neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) including non-steroidal MRAs, and sodium-glucose contransporter-2 (SGLT2) inhibitors.
- Invasive methods for decongestion, such as renal replacement therapy, should be used as a last resort when managing cardiorenal syndrome.

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